

NIEHS News

Women's Health Research at NIEHS

The fact that the majority of the population, women, are understudied in biomedical science remains a scientific anomaly, one that the National Institutes of Health has resolved to remedy. Within NIH, NIEHS has a long history of interest in women's health including studies on diethylstilbestrol, estrogens in the environment, cancer, fertility, and reproductive health. Today, NIEHS approaches women's health with a renewed emphasis, with an even greater dedication not only to disease and dysfunction relating to women and their reproductive role, but to those illnesses disproportionately affecting women such as breast cancer, osteoporosis, endometriosis, leiomyoma (fibroid tumors), and lupus.

The "NIEHS News" section of this issue focuses on NIEHS initiatives in women's health, highlighting various diseases and dysfunctions disproportionately affecting women and discussing NIEHS research directed at those concerns.

The importance of a women's health agenda is driven by three facts: Over a lifetime, women's health is generally worse than men's, certain health problems are more prevalent in women than in men, and certain health problems are unique to women or affect women differently than men. Knowledge concerning the causes, expression, and treatment of many diseases has frequently been derived from studies of men under the assumption that there are no significant sex-based differences, even though, for example, cardiovascular disease accounts for a higher percentage of deaths among women than men in all stages of life. In regard to death from gender-specific disease, nearly one-third of all cancer deaths in women are due to malignancies of the breast, ovary, uterine cervix, and uterine endometrium. Approximately one in nine women will be diagnosed with breast cancer during her lifetime.

The general health of women is dramatically affected by nonfatal diseases and dysfunctions. Frequently occurring diseases that are unique to women include endometriosis and leiomyoma of the uterus, which affect up to 20–30% of the female population and for which the causes remain obscure. Among diseases common to both sexes, women suffer inordinately from osteoporosis, which affects a majority of women over age 60, and from immunologic disorders including rheumatoid arthritis, diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, and

autoimmune thyroid diseases, all of which are more prevalent in women than in men. In addition, neurologic conditions such as Alzheimer's disease and various affective disorders are more common among females.

As increasingly more women enter the workforce, they may be exposed to a variety of occupational chemicals and hazards that may lead to adverse health and reproductive effects. In addition, smoking, alcohol consumption, and other lifestyle factors play an increasingly important role in determining the health status of women. There is now abundant evidence that environmental factors may contribute to many of the disease processes discussed above. Some examples of likely environmental impact on women's health include the following:

- Among the most widespread and persistent environmental toxicants are chlorinated hydrocarbons (such as DDT and polychlorinated biphenyls), which are known to possess estrogenic potential, i.e., the ability to mimic the biological effects of estrogens. Imbalanced or unopposed estrogen exposure is a leading risk factor for many gynecologic malignancies, as well as benign proliferative disorders such as endometriosis and leiomyoma. The potential impact of these compounds on hormone-dependent physiological processes such as conception and fetal development, as well as on disease processes such as osteoporosis and cardiovascular disease, demands further exploration.
- Many environmental toxicants are lipophilic, resulting in accumulation in fatty tissue. Because women have a greater percentage of body fat than men, they tend to develop a greater body burden of these compounds. Increased health risks are thus realized when fat stores are mobilized, such as during dieting or lactation.
- Women face a unique exposure to pharmacologic agents, such as hormone-based contraceptive formulations that present an uncertain risk for cardiovascular disease and cancer and estrogen replacement therapy that may be associated with an increased cancer risk.
- Environmental exposures may aggravate certain diseases that are more common in women and which are often assumed simply to reflect the inevitable consequences of aging. Heavy metals, for example, have been shown to accelerate osteoporosis, and numerous environmental agents are known to be neurotoxic.

The expanded study of environmental factors in diseases of women is expected to spawn multiple benefits, not only limited to the goal of developing new prevention strategies to decrease disease prevalence and severity. A heightened understanding of the mechanisms through which environmental agents disrupt normal physiologic processes will undoubtedly lead to greater insights into the biological phenomena and mechanisms. Data on such phenomena could then be used to design new disease prevention or treatment strategies. Finally, the benefits from this research will not be limited to women. Progress in the area of reproductive and developmental toxicology translates into better health throughout later life for men and women equally, and history has shown that research endeavors into any area of disease typically yield unexpected findings that benefit all of humanity.

Environmentally Related Cancer in Women

Approximately 27% of all cancer deaths in American women are accounted for by cancers of the breast (44,000 per year), ovary (12,500), uterine endometrium (5,500), and uterine cervix (4,500). Among these, breast cancer is by far the biggest killer, and the death rate from this disease increased by a disturbing 24% between 1979 and 1986. Although significant progress has been made in defining genetic factors involved in breast cancer, the role of environmental influences remains largely unexplored. This is particularly troubling since the recent increase in breast cancer incidence is likely to involve environmental rather than genetic factors. Abundant epidemiologic and experimental data support the probable role of environmental factors and chemical carcinogens in the etiology of breast cancer. Currently, several intramural and extramural research groups are actively pursuing aspects of breast carcinogenesis, including studies on individual differences in carcinogen-metabolizing enzymes and breast cancer susceptibility, the definition of steroid hormone growth-regulatory pathways in the mammary gland, the identification of genetic loci involved in breast cancer development, and the role of fat-soluble pesticides as breast carcinogens. Several opportunities exist for expanding these research efforts, especially in regard to the interplay of environmental factors and genetic susceptibility in the etiology of breast cancer.

Ovarian cancer is a relatively common and highly lethal disease: more than 60%

of the women diagnosed with ovarian cancer will die prematurely as a result. Little is known of the causes of ovarian cancer; epidemiologic studies suggest that menstrual, environmental, and genetic factors are important. Evidence for the role of environmental factors is primarily population based and suggest that dietary factors and chemical carcinogens are contributors to increased risk. The intramural and extramural NIEHS expertise in the areas of chemical carcinogenesis and growth factor biology, along with ongoing research projects in the area of genetic predisposition to ovarian cancer, provide the foundation for an expanded and productive research agenda in this area.

Endometrial carcinoma is the most frequently diagnosed gynecologic malignancy in the United States, but remains the least studied of the major cancers affecting women. Unlike cancers of the breast and ovary, endometrial cancer is limited primarily to women over the age of 50, and well-established risk factors suggest probable etiologic factors, most relating to estrogen. Researchers at NIEHS have used molecular genetic approaches to distinguish etiologic factors and animal models (including transgenic mice) to understand the role of physiologic and environmental factors in endometrial carcinogenesis.

Diethylstilbestrol as a Model for Environmental Estrogens

The health effects of diethylstilbestrol (DES) exposure are a research priority that reflects the convergence of several related investigative projects that are major areas of concern for NIEHS. The synthetic estrogen DES was administered to pregnant women during the 1940s through 1960s, originally for high-risk pregnancies but later to promote "healthier babies" as well. Subsequently, the drug was linked to the development of an otherwise extremely rare malignancy, clear-cell carcinoma of the vagina, in young female offspring exposed *in utero*. In addition, a number of more common non-neoplastic changes in the reproductive tract of DES-exposed daughters were identified, including vaginal adenosis, cervical ectropion, and numerous other structural abnormalities. Although the public health hazards associated with further exposure to DES have been largely eliminated, there are a number of compelling reasons for the continued study of DES-exposed women, as well as for basic research on the biological effects of DES and other environmental estrogenic compounds.

First, it is unclear whether the human cancer incidence resulting from DES exposure has peaked. Although the majority of DES daughters have passed the age range

for vaginal carcinoma development, few have reached the age range (postmenopausal) in which endometrial carcinoma typically occurs in the DES unexposed population, and endometrial carcinoma occurs with a much higher prevalence than vaginal carcinoma in DES-treated mice. Similarly, the threat of breast cancer is still a concern in this population. The identification of molecular genetic markers for DES carcinogenicity is therefore a continuing priority; such markers would also be of value in predicting risk for third-generation DES offspring, for whom little is known about potential health risks.

Second, DES may be viewed as a model compound for other environmental agents with estrogenic potential. The bioaccumulation of these environmental estrogens is recognized as a problem of increasing magnitude, and certain human populations in the United States have been shown to carry amounts of these fat-soluble compounds which, in fish and other wildlife, cause significant endocrine dysfunction and developmental anomalies of the reproductive tract. Insights into the biological effects of DES should therefore provide a foundation upon which future environmental health problems may be effectively addressed.

NIEHS has a long history of accomplishments in conducting and supporting research on estrogen action, hormonal carcinogenesis, and other types of estrogen-related pathology, particularly for DES and similar compounds. More recent achievements have provided insights into basic mechanisms of estrogen receptor action at the molecular level. A transgenic mouse that overexpresses the estrogen receptor is being developed to study tissue susceptibility and mechanisms for hormonal carcinogenesis. New endeavors include the analysis of human and animal tumors resulting from DES exposure *in utero* for molecular genetic alterations. Rapid advances in the fields of molecular and developmental biology have provided numerous insights into relevant genes and molecular pathways involved in reproductive tract development. Epidemiologic studies are focused on a broad range of health effects among DES-exposed men and women. Expanded research efforts are necessary to use this knowledge in exploring the epigenetic effects of DES in relation to reproductive tract malformations at the molecular level.

In addition to the estrogen receptor, research on the role of "orphan receptors" in environmental disease is promising. Identification and characterization of orphan receptors and their endogenous ligands will provide a link to understanding the molecular mechanisms through which

exogenous chemicals may exert toxic effects and through which natural substances influence physiologic processes. For example, a recently discovered member of the nuclear receptor family apparently recognizes a class of foreign chemicals called peroxisome proliferators, which includes industrial plasticizers, herbicides, and hypolipidemic agents. Similarly, a receptor from another gene family exists for the ubiquitous xenobiotic dioxin, or TCDD. A related example is the retinoids, which regulate differentiation and growth of a variety of epithelial tissues including mammary gland, cervical, vaginal, and uterine epithelium. Ongoing research at NIEHS is directed toward understanding the process of squamous differentiation in gynecologic epithelial tissues by retinoids and estrogens, and interactions between the retinoic acid receptor and estrogen receptor signaling pathways. Further research is necessary to define these pathways at the molecular level and to elucidate possible therapeutic applications of retinoids in breast and other cancers.

Role of the Environment in Osteoporosis

Osteoporosis is a complex disorder of the skeletal system characterized by decreased bone mass, which leads to increased skeletal fragility and fracturing. The pathogenesis of this metabolic disorder is likely to be multifactorial, involving genetic, racial, and environmental factors including smoking, diet, and alcohol. Interactions between the endocrine and immune systems appear to play a key role in maintaining the physiological homeostasis in bone metabolism. Exposure to estrogenic substances, a number of which are widespread in the environment, can influence bone pathology, as can exposure to heavy metals. Researchers at NIEHS are using cell culture and animal studies to investigate the molecular mechanisms of estrogen receptor-mediated effects on bone development and metabolism, and NIEHS-supported studies are investigating the role of metals such as aluminum and cadmium in osteodystrophies. Important questions remain regarding the competition of these metals with calcium in bone deposition and reabsorption. Because the condition appears to be more severe in women without ovarian activity (e.g., postmenopausal), understanding the modulatory effects of estrogens on heavy-metal toxicity may contribute to our knowledge of the process of osteoporosis.

We now know, that early exposure to DES at very low doses can affect bone density. Basic and clinical studies are now focusing on the potential role that dose and time of exposure to estrogenic sub-